REMARKS

Claims 98-102 stand as originally entered in the Amendment filed on May 12, 2003; no amendments have been filed following the final rejection of Claims 98-102.

Claims 98-102 stand rejected under 35 U.S.C. §101 as allegedly not supported by a specific and/or substantial asserted utility or a well established utility. Claims 98-102 also stand rejected under 35 U.S.C. §112, first paragraph, the claims allegedly not being supported by a specific and/or substantial asserted utility or a well established utility so that one skilled in the art would not know how to use the claimed invention. Applicants respectfully traverse these rejections.

Summary Of Arguments

In the following detailed arguments, Applicants will show that the Examiner has failed to make a *prima facie* case of lack of utility that is the requisite basis for these rejections, and so these rejections are improper. Failing to make the *prima facie* case, the burden has not shifted to the Applicants so as to require Applicants to make a case in rebuttal. However, even though there is no legal requirement to do so, Applicants also show that the specification teaches at least one specific, substantial, and credible asserted utility for the claimed invention, as required by 35 U.S.C. §101.

Despite the assertions of utility made in the specification (*e.g.*, at pages 18, 28-29, and 55-57 as discussed above), the Examiner assumes that an "orphan receptor" necessarily lacks utility, and concludes that "further experimentation is necessary at the time of filing the instant invention to attribute a function and 'real world" utility to the claimed nucleic acid molecules" (Office Action dated July 24, 2002, page 4, lines 11-17). However, it was known in the art, and demonstrated in the specification as filed, that knowledge of a *native* ligand is not a pre-requisite for utility of a receptor.

Multiple examples of specific and substantial uses for the claimed nucleic acids, vectors, cells and processes are asserted in the specification. The specification as filed asserts and/or demonstrates utility including, for example, cell activation, treatment of disorders of the peripheral nervous system using ligands to GFRα3, ligand screening, and other uses. In addition, Applicants will show that the claimed invention has inherent utility, which is now recognized in the art, and for this reason as well satisfies 35 U.S.C. §101.

Applicants will further show that the specification teaches how to use the invention by providing the specific, substantial, and credible utility as discussed above, and by providing ample examples of how to practice the invention without the need for undue experimentation. Thus, such uses being taught in the disclosure, Applicants will show that the requirements of 35 U.S.C. §112, first paragraph, are also fulfilled.

Consequently, Applicants submit that all outstanding rejections are overcome and should be withdrawn.

A. The Rejection of Claims 98-102 Under 35 U.S.C. §101 as Being Directed to an Invention That is Not Supported by a Specific and/or Substantial Asserted Utility or a Well Established Utility is Improper and Should be Withdrawn.

1. A prima facie case of lack of utility has not been established

Utility – Legal Standard

The patent statutes provides that a patentable invention be "new and useful":

35 U.S.C. §101

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible asserted utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in

certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an Applicant has identified for the invention* that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II (B) (1) gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. §2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Compliance with 35 U.S.C. §101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the U.S. Patent and Trademark Office (PTO) must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the PTO has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant. The issue will then be decided on the totality of evidence.

Proper Application of the Legal Standard

Applicants having asserted a specific, substantial and credible utility for the claimed invention, the Examiner has the burden of rebutting that utility.

The Examiner states: "Therefore, because no known specific biological activity is described within the instant specification nor specifically associated with any nucleic acid that encodes the polypeptides of SEQ ID NO:17, because the specification merely discloses on page 55 that the human 'GFRα3 does not bind any of these [GDNF family member] molecules (Figure 9C)', and that 'GFRα3 is thus an orphan receptor', the claimed polynucleotides have no specific nor substantial utility because further experimentation is necessary at the time of filing the instant invention to attribute a function and 'real world" utility to the claimed nucleic acid molecules" (Office Action dated July 24, 2002, page 4, lines 11-17).

Applicants respectfully disagree with the Examiner's characterization of the present invention, and submit that the Examiner failed to apply the proper legal standard when making the rejection.

In contrast to the Examiner's assertion, Applicants note, as discussed above, that the specification teaches specific biological activity. For example, the specification teaches that the novel GFRα3 molecules can dimerize, and that such dimerization can activate a kinase domain, and so be used to measure ligand-induced α- subunit receptor activation (page 4, lines 24-27; page 55, line 10-page 56, line 22). The specification teaches GFRα3 ligands (see, *e.g.*, page 56, lines 23-38 to page 57, lines 1-13). Ligand-mediated activation of (chimeric) GFRα3 receptors is disclosed (see, *e.g.*, page 55, lines 31-37 to page 56, lines 1-22; page 57, lines 15-38 to page 58, lines 1-32). Ligands to GFRα3 are explicitly said to be useful for treatment of diseases or conditions of the peripheral nervous system (see, *e.g.*, pages 28, lines 34-38 and 29, lines 1-14).

Applicants note that it is not legally required to disclose "a known *biological activity*" for a protein in order to establish utility for the encoding nucleic acid. According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible asserted utility" or a "well-established utility."

There is nothing in the applicable law and case law that would require that Applicants establish a substantial and specific *biological activity* for a polypeptide in order to meet the utility requirement of the patent statute.

An applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974); *see, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

There is no legal requirement that applicant must know the way his or her invention works in order to establish utility. Indeed, it is well established that "[an] inventor need not understand precisely why his invention works" (*Parker v. Frilette*, 462 F.2d 544, 547, 174 USPQ 321, 324 (CCPA 1972)). Accordingly, the presumption of specific, substantial and credible asserted utility stands, and the burden to provide further evidence of utility has not shifted to Applicants.

Applicants note that it is improper to overlook or ignore these asserted utilities in the mistaken belief that a patent applicant must demonstrate a "currently available" use; as dictated by applicable case law and reflected in the Guidelines cited above, Applicants' assertion of a credible utility for the claimed invention is to be accepted (*e.g.*, M.P.E.P. §2107 II (B) (1) cited above). The only conceivable reason for the fact that the Examiner overlooks these utilities is that he is looking for a "currently available" use, instead of accepting Applicants' assertion of a series of credible utilities, as dictated by applicable case law and reflected in the Guidelines cited above.

Moreover, the Examiner failed to advance any evidence or solid scientific arguments why the uses disclosed by Applicants would not have been considered reasonable as of the priority date of this application, or would not provide any public benefit. Indeed, contrary to the warning of M.P.E.P. §2107.01, the Examiner clearly applies the erroneous requirement that the invention be currently available to the public in order to meet the utility requirement. As discussed above, Applicants' assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. The Examiner presented no solid scientific arguments or any evidence of such reason. The fact that the native ligand for the

GFRα3 receptor was not identified at the time the present invention was made is not sufficient reason for the conclusion that GFRα3 receptor itself had no patentable utility at the relevant time, particularly in the face of explicit disclosure in the application of data showing utility and explicitly asserted utility in the specification.

Characterizing GFRα3 as an orphan receptor, the Examiner suggests that since "'GFRα3 is thus an orphan receptor', the claimed polynucleotides have no specific nor substantial utility because further experimentation is necessary at the time of filing the instant invention to attribute a function and 'real world' utility to the claimed nucleic acid molecules" (Office Action dated July 24, 2002, page 4, lines 14-17). However, characterization of a receptor in such a way provides no indication of its utility or lack thereof. In fact, the pharmaceutical sciences and medicine provide many examples of useful drugs and therapeutics which act on receptors with unknown or uncharacterized native ligands, or whose native ligands were unknown at the time that useful functions for, or artificial ligands to, the receptor were identified.

For example, the orphan receptor erbB2 (also known as c-erb2 and HER2) does not have a known *native* ligand and so is an orphan receptor: "ErbB2/Her2 is an orphan receptor that does not bind ligand alone but heterodimerizes with the other ErbB receptors for NRG [neuregulin] signaling." (Negro et al., "Essential roles of Her2/erbB2 in cardiac development and function," Recent Prog Horm Res. **59**:1-12 (2004), page 1, lines 7-8.) Yet, despite its being an "orphan receptor," ErbB2 expression is used in the diagnosis of breast cancer and in the determination of a proper therapy for that disease. "ErbB2-overexpressing cancers usually are associated with a poor prognosis and account for about 30% of metastatic breast cancer in women." (Negro et al., page 2, lines 26-28.) Moreover, the breakthrough drug HERCEPTIN® (trastuzumab) binds to that orphan receptor and has been found to be effective in treating many women suffering from breast cancer. "Trastuzumab, administered as single-agent, first-line therapy in women with HER-2 overexpressing metastatic breast cancer ... produces durable objective response and is well-tolerated. In combination with chemotherapy, improvements in response rate, time to progression, and survival occur in women with HER-2 overexpressing metastatic breast cancer." Esteva, "Monoclonal Antibodies, Small Molecules, and Vaccines in the Treatment of Breast

Cancer," *The Oncologist* **9(Suppl 3)**:4-9 (2004), page 6, column 1, lines 8-16). See also, for example, US Patent 6,627,196 to Baughmann et al. and citations therein (e.g., columns 1-4).

ErbB2 is not an isolated example of an "orphan receptor" that is useful. For example, receptors highly specific for growth hormone secretogogues (synthetic molecules that affect release of growth hormone) have been known for many years, as have been synthetic ligands to them. Activation of these receptors by synthetic ligands can increase appetite and reverse age-related decline in growth-hormone secretion in aged patients (Smith et al., "Growth hormone secretogogues: prospects and potential pitfalls," *Best Pract Res Clin Endocrinol Metab.* **18(3)**:333-347 (2004)). However, it was only long after the discovery of these receptors and of artificial ligands that activate them that a native ligand for such receptors was identified (named "ghrelin"). As stated by Rosická et al.: "Ghrelin is a new endogenous peptide discovered during the search for an unknown endogenous ligand of a receptor of known structure and function." (page 439, "Ghrelin - a New Endogenous Growth Hormone Secretogogue," Physiological Research **51**:435-441 (2002); emphasis added).

Thus, mere characterization of a receptor as an "orphan receptor" in no way indicates that no function or use can be ascribed to that receptor. Mere characterization of a receptor as an "orphan receptor" in no way indicates that more experimentation need be done in order to determine a use for the receptor. As demonstrated by the examples discussed above, "orphan receptors" having no known native ligand have proven to be clinically important and useful. Such specific uses, proven in the clinic as well as the research laboratory, are clearly credible and substantial. Accordingly, mere characterization of a receptor as an "orphan receptor" cannot support an allegation of lack of utility under 35 U.S.C. §101.

Applicants submit that the Examiner's position is both legally and technically incorrect. In conclusion, the Examiner has not shown *prima facie* why a skilled person would not have accepted the specific asserted utility disclosed in the application as filed.

2. The application discloses specific, substantial and credible utility

Specific, Substantial, and Credible GFRα3 Utility is Disclosed in the Application

The present application, and both provisional applications from which priority is claimed, assert specific, credible and substantial utility for the novel GFRα3 receptor disclosed in the application, and thus the Applicants have met the required legal standard.

The GFRα3 receptors and GFRα3 ligands taught by the Applicants are useful for treating diseases and conditions of the peripheral nervous system, identifying compounds for treatment of diseases related to GFRα3 receptors, and for identifying tissues expressing GFRα3 receptors. Such asserted uses are significant and promise to contribute to the health and well-being of those suffering from such diseases and conditions.

As discussed above, specific and substantial uses for the claimed nucleic acids, vectors, cells and processes include, for example, treatment of diseases or conditions of the peripheral nervous system such as peripheral neuropathies (for example, at pages 28, lines 34-38 and 29, lines 1-14) and the stimulation of proliferation, growth, survival, differentiation, metabolism, or regeneration of GFRα3- and Ret-containing cells (see, *e.g.*, page 18, lines 28-29). In addition, Applicants provide GFRα3 ligands (see, *e.g.*, page 56, lines 23-38 to page 57, lines 1-13) and disclose their utility (see, *e.g.*, the disclosure of ligand-mediated activation of (chimeric) GFRα3 receptors in Example 10, page 55, lines 31-37 to page 56, lines 1-22 and Example 12, page 57, lines 15-38 to page 58, lines 1-32). In addition, Applicants teach the use of nucleic acids encoding GFRα3 (or their complement) as, for example, hybridization probes in chromosome and gene mapping, tissue distribution studies, and in the generation of anti-sense RNA and DNA (see, *e.g.*, pages 27-29).

The specification further teaches specific biological activities. For example, at pages 28, lines 34-38 and 29, lines 1-14, ligands to GFRα3 are explicitly said to be useful for treatment of diseases or conditions of the peripheral nervous system such as "peripheral neuropathies associated with diabetes, HIV, chemotherapeutic agent treatments" and neuropathic pain. Such asserted utilities "are consistent with the data of Example 5 in which a strong expression of GFRα3 within the developing and adult sensory ganglia was observed" (specification, page 29, lines 1-2). In addition, consistent with the expression data disclosed in the specification, further

uses include treatment of conditions of the autonomic nervous system and of the sympathetic nervous system, as discussed on page 29, lines 3-8. Applicants also disclose that the present invention provides an advantage derived from the "surprising, relative lack of expression of GFRα3 in many organs, including notably brain, gut and kidney indicates that the ligand (and other agonists and antagonists) which binds this receptor lacks some side effects which may be associated with ligands which bind to GFRα1 and GFRα2 (GDNF and neurturin)" (page 29, lines 9-11). In addition, the inventors disclose that the novel receptors may be used in screening ligands (such as antibodies) for activity (which may be agonist activity or antagonist activity; see, *e.g.*, page 56, lines 19-22).

These activities and uses are also taught in the provisional applications from which the non-provisional application claims priority. For example, U.S. Provisional Patent Application Serial Nos. 60/079,124 and 60/081,569 discuss tissue distribution of GFRα3 (page 43, lines 12-27 and page 44, line 1 to page 45, line 9); antibodies to GFRα3 on pages 30-37; the use of GFRα3 antibodies on page 37, lines 2 to 29 and page 57, lines 1-27; chimeric receptors including GFRα3 and their activation (page 52, line 8 to page 52, line 26); vectors (page 45, lines 14-23 and page 46, lines 14-18) and host cells (page 20, lines 2-11) comprising GFRα3 message; and the treatment of diseases or conditions of the peripheral nervous system on page 4, lines 14-16 and on page 30, lines 1-24.

Applicants note that antibodies may be ligands: *i.e.*, may act as agonists or antagonists to receptors to activate, or to inhibit, the action of their target receptors. Antibody agonists were known at the time of filing the application (see, *e.g.*, Eur. J. Immunol. **27(5)**:1108-1114 (1997) Thilenius et al., "Agonist antibody and Fas ligand mediate different sensitivity to death in the signaling pathways of Fas and cytoplasmic mutants," a reference submitted with the response mailed on July 2, 2004, but not entered). Such agonists were explicitly discussed in the specification as filed (see, *e.g.*, page 57, lines 16-19). Applicants in fact demonstrated binding of ligands to (chimeric) GFRα3 receptors (page 56, lines 3-22). The specification further teaches GFRα3 ligands that are antibodies to GFRα3. The inventors disclose that ligands (such as antibodies) may be screened for agonist activity against these receptors (page 56, lines 19-22). Thus, specific biological activity for the GFRα3 receptor is taught in the application as filed.

Thus, Applicants submit that the utility disclosed and asserted in the application is specific and substantial, as shown by the specific statements in the specification as discussed above (see also, *e.g.*, page 28, lines 34-38 to page 29, lines 1-14; page 56, line 23 to page 58, line 32).

Moreover, the utility asserted in the application is credible. The specification states, and it was recognized in the art at the time, that a receptor may be bound by a ligand; such binding is useful to activate the receptor, or to inhibit its action, to label it, and in other ways. Thus, one of ordinary skill in the art at the time the application was filed would know from the disclosure, and would accept, that the novel GFRα3 molecules disclosed in the application were useful as receptors with biological activity. The law does not require the identification of a *natural* ligand to establish utility for a receptor. Nor is identification of a *native* ligand needed to provide utility in practice: as discussed above, for example, erbB2 and ghrelin receptors, and artificial ligands to these receptors, have benefited human patients, without identification of a *native* ligand to these "orphan receptors." Indeed, Applicants use the term "ligand" in a broad sense, not limiting its meaning to a native ligand of GFRα3 (see, *e.g.*, page 15, line 36 to page 16, line 2, and page 16, lines 8-10).

The asserted specific and substantial utility is based, in part, upon the results of assays disclosed in the Examples (*e.g.*, Examples 9, 10 and 12), upon the GFRα3 tissue localization discovered by Applicants, and other findings disclosed in the specification. Such findings demonstrate that the GFRα3 receptor interacts with a β-subunit receptors as expected, and is functional when expressed in cells in culture, and that it is found in specific tissues identified by the Applicants, indicating specific functions that could be useful in treating diseases related to those tissues. The logic underlying the asserted specific and substantial utility is not seriously flawed, therefore, one skilled in the art would have found the stated utility "credible" at the effective filing date of the application.

Moreover, such utility has been confirmed by subsequent publications. For example, a subsequent publication by one of the inventors (Andres et al., " Multiple effects of artemin on sympathetic neurone generation, survival and growth," Development **128(10)**:3685-3695 (2001)) confirms that the novel receptor GFRα3 is important in the generation, survival and growth of

peripheral neurons in culture. Furthermore, as indicated by Baloh et al. ("Artemin, a novel member of the GDNF ligand family, supports peripheral and central neurons and signals through the GFRalpha3-RET receptor complex," Neuron **21**: 1291-1302 (1998)) the natural ligand for GFRα3 has been subsequently identified and named "artemin." Artemin binds both GFRα3 and the chimeric receptor fusion protein gD-GFRα3-Rse-gD (page 56, lines 17-19). Thus, corroboration and support for the asserted utility of the claimed invention is found in subsequent publications and further shows that the invention has real world utility.

Accordingly, Applicants submit that the specification as filed disclosed specific, substantial and credible utility for the novel GFRα3 receptor discovered by the inventors.

This later-published work discussed above supports the specific, substantial and credible utility as disclosed and asserted in the parent provisional applications and in the present application, and inures to the benefit of the present application. "Inurement involves a claim by an inventor that, as a matter of law, the acts of another person should accrue to the benefit of the inventor." *Cooper v. Goldfarb,* 154 F.3d 1321, 1331, 47 USPQ2d 1896, 1904 (Fed. Cir. 1998). In a patent infringement case where the question of whether conception occurred before confirmatory testing was an issue, the Federal Circuit discussed testing performed by others prior to filing a patent application, and stated that "because the testing confirmed the operability of the inventions, it showed that Burroughs Wellcome inventors had a definite and permanent idea of the inventions. It was part of the reduction to practice and inured to the benefit of Burroughs Wellcome." (*Burroughs Wellcome Co. v. Barr Laboratories*, Inc., 40 F.3d 1223, 1230, 32 USPQ2d 1915, 1922 (Fed. Cir. 1994)). The testing that was found not to have been necessary for conception of the invention occurred before the filing of a patent application, so that the court, not deciding a case in which the filing of a patent application provided constructive reduction to practice, was also interested in reduction to practice in the Burroughs case.

Thus, where, as here, the Applicants have disclosed a novel receptor; have demonstrated activation of chimeric receptor constructs by non-natural ligands of the novel receptor; have stated that it has a natural ligand, and have disclosed the identity of the later-discovered natural ligand in the filed application itself; then, the expected identification of the natural ligand inures to the Applicants and serves to support the specific and/or substantial asserted utility or a well

established utility as required by 35 U.S.C. §101. Such support is in concert with, and in addition to, the other uses demonstrated in the application as discussed previously and discussed above.

Applicants submit that the utility disclosed in the application, alone and when taken in view of subsequent publications, demonstrates a specific, substantial and credible asserted utility as required by 35 U.S.C. §101.

3. The claimed nucleic acids have inherent utility that is specific and substantial

Applicants further submit that, even were the above arguments not to be accepted by the Examiner, the GFRα3 receptor has inherent utility.

Applicants submit that, in the present case, it is useful to consider the analogous situation of anticipation by inherency. Recent case law in the area of inherent anticipation has held that if a person of ordinary skill in the art, presented with all facts, would understand that the missing structure, composition or function is always necessarily present in the cited prior art, a holding of anticipation by inherency is proper. It is not required that prior to the invention one skilled in the art recognized the presence of the inherent structure, composition or function. The objective understanding of the presence of the inherent structure, composition or function can occur later. *Atlas Powder Co. v. Ireco Inc.* 190 F.3d 1342, 51 USPQ2d 1943 (Fed. Cir. 1999); *Schering Corporation v. Geneva Pharmaceuticals, Inc.* 67 USPQ2d 1664 (Fed. Cir 2003).

The GFRα3 receptor discovered and disclosed by Applicants, by its nature, is effective to bind ligands (whether natural or otherwise) and to affect cells in which it is expressed. It is well-known in the art that a ligand receptor binds ligands, and may be activated by such ligand-binding to induce an effect in the cell or cell membrane in which it is found (see, *e.g.,* page 2, lines 18-33 of that application). For example, it was known at the time the application was filed, and disclosed in the application, that receptor proteins may dimerize with a signaling component to link ligand binding with biological activation in a cell or cell membrane (see, *e.g.,* page 55, lines 11-17). The GFRα3 receptor was described in the application as being useful for antibody formation, treatment of disorders of the peripheral nervous system (using ligands to GFRα3, such

as antibody ligands), cell activation, production of chimeric receptors, ligand screening, and other uses as discussed above.

Since such actions are inherent in the receptor itself, then such uses are inherent in the receptor itself. Receptor activation or inhibition upon ligand binding was well known in the art at the time of filing the application. These actions being inherent in the receptor, disclosure of the GFRα3 receptor was effective to provide these asserted utilities to the public. These actions being inherent in the GFRα3 receptor, and being specific to that receptor, the specification therefore discloses specific utility for the receptor. Since the effects of ligand binding on receptors was well known, such asserted utility would be credible. Such uses are substantial, providing such "real world" uses as treatments of diseases or conditions of the peripheral nervous system. Accordingly, taken from the perspective of one of ordinary skill in the art, Applicants' disclosure provides a reasonable use that is specific, substantial and credible.

Thus, the ability of the novel GFRα3 receptor discovered by the Applicants to bind and to be affected by ligands is inherent in the receptor itself, and was recognized as such by the Applicants (*e.g.*, page 56, lines 5-6 "an assay to identify agonist antibodies and a natural ligand (or other agonists) for mammalian GFRα3 follows the method described above for GFRα2-Rse"). The natural ligand was subsequently discovered, as noted in the specification (page 56, lines 17-18). The binding activity of the novel GFRα3 receptor was disclosed in the application to be useful for specific purposes (*e.g.*, page 30, lines 11-14, treatment of disorders of the peripheral nervous system).

Thus, the Applicants have disclosed a novel receptor; have demonstrated activation of chimeric receptor constructs by non-natural ligands of the novel receptor; have stated that it has a natural ligand, and have disclosed the identity of the later-discovered natural ligand in the filed application itself. Applicants submit that the expected identification of the natural ligand inures to Applicants and serves to support the specific and/or substantial asserted utility or a well established utility as required by 35 U.S.C. §101. Such support is in concert with, and in addition to, the other uses discussed previously and discussed above.

Thus, Applicants submit that the utility disclosed in the application, alone and when taken in view of subsequent publications, demonstrates a specific and/or substantial asserted utility or a well established utility as required by 35 U.S.C. §101.

Accordingly, for at least these reasons, Applicants respectfully submit that the rejections of Claims 98-102 under 35 U.S.C. §101 as allegedly lacking a specific and/or substantial asserted utility or well established utility is in error, and should be withdrawn.

B. The Rejection of Claims 98-102 Under 35 U.S.C. §112, First Paragraph as Being Directed to an Invention Lacking a Specific and/or Substantial Asserted Utility or Well Established Utility, so That One of Ordinary Skill in the Art Would Not Know How to Use the Claimed Invention is Improper and Should be Withdrawn.

35 U.S.C. § 112, first paragraph states:

35 U.S.C. §112, first paragraph

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or to which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 98-102 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not being supported by either a specific and/or substantial asserted utility or a well established utility so that one skilled in the art would not know how to use the claimed invention.

Applicants note that the specification includes multiple examples of the utility of the subject matter of Claims 98-102, as discussed above. Thus, the application provides several examples of specific and substantial utility for the present invention and of its use, and thereby teaches how to use the invention. Examples demonstrate such use (*e.g.*, page 55, line 31 to page 56, line 1-22, and page 57, line 15 to page 58 line 32, as discussed above). A person of skill in the art at the time the present invention was made, in view of the teachings of the specification, the general knowledge in the art at the time, and in view of the inherent uses and properties of the claimed nucleic acids, cells and processes would have known how to use the invention.

Thus, for reasons set forth above, the rejections of Claims 98-102 under 35 U.S.C. §112, first paragraph, is in error, and should be withdrawn.

In conclusion, Applicants respectfully submit that, for the above reasons, all outstanding rejections are overcome. As all of the claims in the present application are in condition for allowance, Applicants respectfully request the Examiner to bring all pending claims to issuance.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39766-0065 A**.

Respectfully submitted,

Dated: January 11, 2005

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